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Oral cancer survival- an overview of Dental Surgeon's role

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Abstract

Oral cancer constitutes an important proportion of overall percentage of cancer. Survival rates of oral cancer is relatively low in comparison to major cancers, although incidence rate being as less as 3 percent of the cancers. Delay in diagnosis, cancer metastases, and presence of secondary tumors are the main reasons for the poor prognosis of oral cancer. Innocuous potentially malignant lesions have higher chances for malignant transformation and early diagnosis of these lesions is necessary for the better survival rates. Patient's overall outcome can be improved through early diagnosis and management of these potentially malignant lesions, as the oral cavity can be easily examined. Currently available clinical diagnostic tools developed for the early detection of oral cancer include toluidine blue dye (TB) (tolonium chloride), Oral brush biopsy, chemiluminescence using Vizilite, salivary diagnostics, and several imaging devices such as Velscope and multispectral optical imaging systems. This paper deals in detail about the various diagnostic aids in detection of oral cancer, thus emphasising dentist's role in combating this dreadful entity.

Keywords: Oral cancer, Toluidine blue staining, Oral brush biopsy, Chemiluminescence.

Introduction

Head and neck cancer accounts for the sixth most common human cancer,[(1)] and constitutes 3% of all types of cancer.[(2)] Oral cavity is the site of oral cancer in 48% of cases, and oral squamous cell carcinoma (SCC) accounts for 90% of these cancer. Annual occurence of new cases of oral squamous cell carcinoma is more than 300,000[(3)] Annual occurrence of new cases recorded in the US, EU and Japan is 35,000; 40,000 and 10915 respectively.[(4)] Tongue is the most common site for intraoral carcinoma, constituting around 40% of all intra-oral cases and posterio-lateral border and ventral surfaces of the tongue being the preferred sites. Second-most common intraoral location for oral cancer is the floor of the mouth. The gingival, buccal, and labial mucosa, and hard palate are the less common sites. According to various studies head and neck cancer, particularly tongue cancer is showing an increase in rate of occurrence among young adults.[(5)] Oral carcinomas result in approximately 9,000 deaths annually. According to the American Cancer Society screening protocol for cancers of the head and neck (including oral cancers), asymptomatic individuals between the ages of 20 and 40 should be screened every three years and asymptomatic individuals after age 40 should be screened yearly. High risk individuals at such as smokers and alcohol abusers should be examined every year regardless of their age.[(7)] The detection of oral cancer in early stages is quite difficult and any procedure that facilitates visualization of suspicious lesions may be fruitful in early detection. Alterations in the surface texture, integrity, color, size and contour, and mobility of structures indicates a suspicion for potentially malignant disorders or squamous cell carcinoma.[(8)] However, only a small fraction of these lesions undergo malignant change and an unaided oral examination unfortunately fails to distinguish between lesions that are potentially dangerous from lesions that are benign. The development of potentially useful diagnostic tools at the clinical and molecular level for the early detection of oral precancer is the result of recent advancements in oral cancer research. However, the gold standard for oral cancer diagnosis remains tissue biopsy with a pathologic assessment.[(9)]

Various clinical diagnostic tools for the early detection of oral pre-cancer includes –

1. Vital staining (toluidine blue dye, lugol's iodine staining, methylene blue staining)
2. Oral CDx brush biopsy kits
3. Chemiluminescence (Vizilite)
4. Tissue fluorescence imaging (Velscope system)
5. Tissue fluorescence spectroscopy
6. Salivary biomarkers
7. Optical coherence tomography(OCT)
8. DNA ploidy
9. Tissue Biopsy[(10,11)]

Discussion

Potentially useful diagnostic tools for the early detection of oral precancer and cancer are the result of advancements in research. Various diagnostic tools at the clinical and molecular levels are-

1. Vital staining

A. Toluidine Blue

Tolonuim chloride also known as Toluidine blue (TB) has been used in the past for the detection of mucosal abnormalities of the cervix and the oral cavity. TB is an acidophilic metachromatic dye that has an affinity to selectively stain the acidic tissue components, sulfate, carboxylate and phosphate radicals such as DNA and RNA, but not normal mucosa. The nuclei of malignant cells with increased DNA synthesis have an

increased uptake of the dye therefore rapid dye penetration occurs through randomly arranged tumor cells.

The subject is asked to rinse the mouth with the dye. Afterwards subject is inspected for the areas of blue staining. Depending on the degree of dysplasia, malignant lesions stain dark blue and dysplastic lesions stain with different shades of blue. (8) Blue staining in a patient is indicative of biopsy. Occasionally, the normal mucosa or rough or keratin surfaces (e.g., dorsum of the tongue, gingival crevices) may retain a small amount of dye, which can be wiped away with acetic acid. Similarly, nonmalignant areas of inflammation occasionally stain with toluidine blue therefore it is mandatory to restain all positive lesions within 14 days to lessen the false positive cases. (Fig 1a-d). This is a highly sensitive and moderately specific for malignant lesions, it is far less sensitive for pre-malignant lesions and false negative rates of up to 58% has been reported.

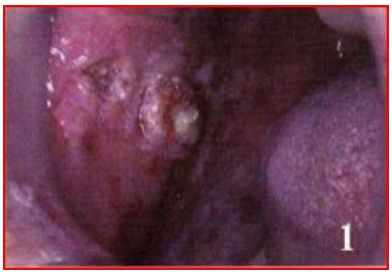

Fig. 1a: Suspected innocous lesion

Fig. 1b: Application of 1% toluidene blue dye

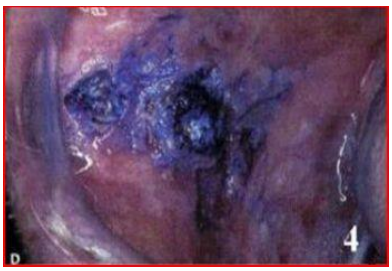

Fig. 1c: Neutralization with 1% acetic acid

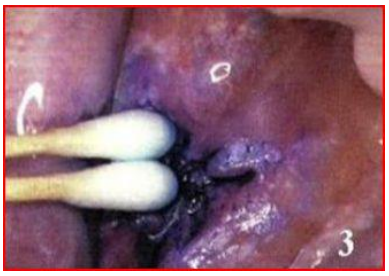

Fig. 1d: Retention of blue color, indicative of malignant lesion

B. Lugol's iodine

An Italian, Camillo Golgi introduced this stain that is formed by adding 2g of iodine and 4g of potassium iodide in 100 cc of distilled water. 1% acetic acid is applied to the lesional tissue for 20 sec. and then rinsed with water. Later, the application of Lugol's iodine for 10-20s at the lesional site with a cotton bud is done.

Lesions retaining brown stain were considered as positive while lesions without retention of stain were considered as negative.[13] The glycogen content present in the normal epithelium forms the basis of the selective staining of the intact mucosa with Lugol's iodine. This selective staining character helps in differentiating the inflammatory or carcinomatous epithelium from the normal epithelium where the glycogen content is low.[14-16]

Staining with toluidine blue (TB) and with Lugol's iodine both (double staining technique) helps in clinical determination of the degrees of differentiation of malignant lesions as poorly differentiated malignant lesions without glycogen content do not show Lugol's iodine retention. Pre-therapeutic assessment of biologic aggressiveness of the disease can also be made by Toluidine blue (TB) with Lugol's iodine. Depending on the retention of the dyes, the biopsy site can be determined.[17] Toluidine blue (TB) and Lugol's iodine may also be used for patients at risk and selecting biopsy sites for patients with wide field cancer.[18]

2. Oral brush biopsy

OralCDx (OralScan Laboratories, Inc.) is a computer-assisted oral biopsy system that collects transepithelial cellular samples. (Fig. 2a) The system contains a specialized brush for the brush biopsy **(**Fig. 2b), a glass slide, a fixative (alcohol/ polyethylene glycol), and a container for sending samples to the CDx laboratory.[19] The procedure involves placement of the brush on the lesion surface and rotating it for 5-10 times till it produces reddening or hemorrhagic spots. (Fig. 2c) The obtained cell material is placed on a dry slide, fixed, and sent for analysis.[20-22] (Fig. 2d) Highly keratinized leukoplakia is a contraindication for the use of this method, as it does not allow enough basal cells to be gathered. Also, inflammatory conditions frequently give atypical results. It is a fast and relatively simple procedure that does not cause bleeding or require anesthesia. Reported sensitivity values ranged from 71.4% to 100% and specificity from 32% to 100%.

Fig. 2a: Oral brush biopsy brush

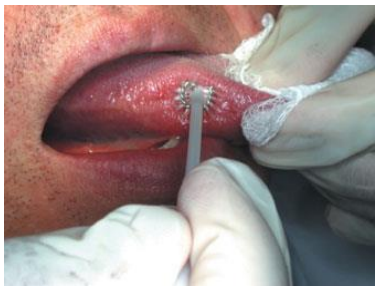

Fig. 2b: Placement of brush on the mucosa to obtain trans-epithelial biopsy

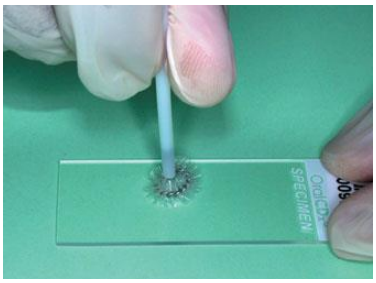

Fig. 2c: Transfer of cells onto glass slide

3. Chemiluminescence (Vizilite)

Chemiluminescence is the emission of light from a chemical reaction.[23] Vizilite, a diagnostic tool for the early oral cancer detection is based on the principle of chemiluminescence. (Fig. 3) The kit contains 1% acetic acid solution, a capsule with an outer shell of flexible plastic, an inner vial of fragile glass and a retractor.[22] Activation requires breakage of the glass vial by bending the capsule. This permits the chemical products to react and produce a bluish-white light with a wave length of 430-580 nm that lasts for around 10 min.[24] The procedure involves a one-minute mouthwash with 1% acetic acid solution. Under diffuse bluish-white chemiluminescent light, normal mucosa absorb the light and appears blue, whereas the light is reflected by abnormal cells (with a higher nucleus: cytoplasm ratio) and by epithelium with excessive keratinization, and/or significant inflammatory infiltrate, which appear acetowhite with brighter, more marked, and more distinguishable borders.[25-27] ViziLite® system enhances the clinician's ability to detect oral lesions, particularly white lesions and also those with white and red areas. The sharp borders between normal and abnormal oral mucosa is easily delineated by ViziLite plus. Also, the borders observed usually extended beyond than those detected in the visual examination.[8,27] Majority of these lesions can be diagnosed with incandescent light, and that mouthwash with acetic acid allowed the additional detection of some lesions.[25] The reported sensitivity is 100% and the specificity ranges from 0%-14.2%.

Fig. 3: Chemiluminescence with vizilite

4. Tissue fluorescence imaging (Velscope system)

Use of tissue autofluorescence has been traced back for the screening and diagnosis of pre-cancers and early cancer of the lung, uterine cervix, and skin. More recently, it has been used in the oral cavity. The changes in the structure and metabolism of the epithelium and sub-epithelial stroma alter their interaction with intense blue light (400 to 600 nm).[10,28] Velscope system is a tissue fluorescence imaging system used for inspection of the oral mucosa.[10,12,29] (Fig. 4) Under the intense blue light (400 to 600 nm), normal oral mucosa emits a green auto-fluorescence, whereas abnormal areas absorb the fluorescent light and appear dark. Hence, early detection of pathological lesions is possible by detecting the early biochemical changes even before their evident appearance. VELscope system seems to be very promising due to its ability and effectiveness in identifying the visually occult lesions and lesions' margins.[29] The sensitivity values ranges from 97% to 98% and specificity from 94% to 100%.

Fig. 4: Autofluorescence with velscope

5. Tissue fluorescence spectroscopy

This system consists of a small optical fiber that produces various excitation wavelengths and a spectrograph that receives, records and analyzes the spectra of reflected fluorescence from the tissue.[10,12,29] This technique accurately distinguishes malignant lesions from healthy oral mucosa with high sensitivity

and specificity.[10,12,29] As the optical fiber can sample only a small mucosal area, this technique is not suitable to detect new lesions or to demarcate large lesions, thus limiting the use of spectroscopy for evaluating well-defined small mucosal lesion that has been already diagnosed through clinical inspection, with the attempt to clarify its benign or (pre)malignant nature[29] (Fig. 5a and b).

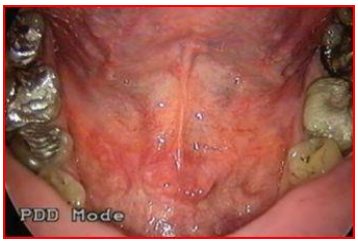

Fig. 5a: Suspected lesion

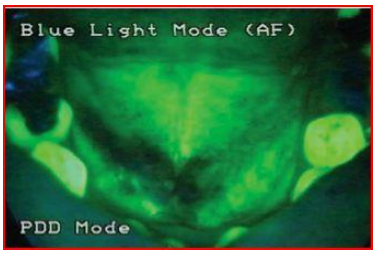

Fig. 5b: Spectroscopy revealing green color, suggestive of malignancy

6. Salivary biomarkers

Saliva may be used as a diagnostic tool for molecular biomarkers for oral cancer detection. Saliva is a mirror of the body and reflects normal and disease states and its use as a diagnostic fluid meets the demands for an economic, easy to collect and non-invasive diagnostic tool. Measurement of specific salivary macromolecules and examinination of proteomic or genomic targets such as enzymes, cytokines, growth factors, metalloproteinases, endothelin, telomerase, cytokeratins, mRNAs, and DNA transcripts can be done by the saliva.[23-32] Cyfra 21-1, TPS, CEA, SCC, CA125, and CA19-9 are the most studied epithelial serum circulatory tumor markers in the saliva of carcinoma patients.

7. Optical coherence tomography

Optical coherence tomography (OCT) is a non-invasive tomographic imaging modality. The technique detects areas of inflammation, dysplasia, and cancer by recording subsurface reflections to build a cross-sectional architectural image of tissue. Contrast enhancement of the images may be done with the use of surface plasmon resonant gold nanoparticles.[33] The imaging range of OCT technology suitable for the oral mucosa is with a tissue penetration depth of 1 mm to 2 mm.[34-36]

8. DNA Ploidy

DNA ploidy measures the nuclear DNA content. The cytological samples after staining with Feulgen dye are compared against a reference group of cells, and a computer-assisted analysis identifies deviations of cellular DNA content. Cancer progression is contributed by genomic instability, and dysplastic lesions are distinguished by abnormal DNA content.[37]

9. Biopsy

Scalpel or punch biopsy and its histopathological evaluation remains the gold standard of diagnosis of potentially malignant disorders. The diagnosis of mild and moderate dysplasia and determination of early-stage invasion of carcinoma *in situ* (CIS) or squamous cell carcinomas (SCC) is dependent upon the variations amongst pathologist's findings.[38,39] Adequate sampling of oral lesions is an important factor for histopathological diagnosis of OSCC. Histopathological changes may be seen even when visual examination fails to detect an oral lesion clinically. (eg. in field cancerization)[39]

Conclusion

Potentially malignant disorders pose a major threat to the overall survival of an individual. Oral health professionals play a major role in early detection and treatment of these disorders, thus combating these dreadful lesions and improving the prognosis. A wide variety of diagnostic aids are currently available which should be used for early detection of these disorders.

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